AD	1

Award Number: DAMD17-02-1-0569

TITLE: Evaluation of DNA Methylation as a Target for Intraductal

Therapy for Ductal Carcinoma In Situ of the Breast

PRINCIPAL INVESTIGATOR: Kristin A. Skinner, M.D.

CONTRACTING ORGANIZATION: University of Southern California

Los Angeles, CA 90033

REPORT DATE: August 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;

Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY	2 DEDORT DATE	2 DEDORT TYPE AND	DATES SOVERE	n	
(Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED Annual (15 Jul 2002 - 15 Jul 2003)			
	August 2003	Aimuai (15 Jul			
4. TITLE AND SUBTITLE		5. FUNDING N			
Evaluation of DNA Methy	lation as a Target for	Intraductal	DAMD17-02-	-1-0569	
Therapy for Ductal Carc	inoma In Situ of the Breas	t '			
6. AUTHOR(S)					
1					
Kristin A. Skinner, M.D	•	•			
•		•			
7. PERFORMING ORGANIZATION NA	ME(S) AND ADDRESS(ES)		8 DERECOMINI	G OPGANIZATION	
University of Southern			8. PERFORMING ORGANIZATION REPORT NUMBER		
Los Angeles, CA 90033		•			
		•			
E-Mail: Kristin.skinner@	med.nyu.edu				
9. SPONSORING / MONITORING			10. SPONSORING / MONITORING		
AGENCY NAME(S) AND ADDRES	S(ES)		1	EPORT NUMBER	
U.S. Army Medical Resea		.mal			
Fort Detrick, Maryland	21702-E012	iiia			
Fore Beeriek, Maryland	21/02-3012				
11. SUPPLEMENTARY NOTES					
12a. DISTRIBUTION / AVAILABILITY	STATEMENT			12b. DISTRIBUTION CODE	
Approved for Public Release; Distribution Unlimited				TEST STOTAL COSE	
1-2-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1	one, production one	.12004			
				<u> </u>	
13. ABSTRACT (Maximum 200 Word	·				
Ductal carcinoma in situ(DC	IS), the preinvasive form o	f infiltrating ductal	breast cancer	r, accounts for 20-30% of	
breast cancers and is treated surgically. In DCIS, the malignant cells are confined within the basement					
membrane. DCIS is a local disease, and so an ideal candidate for local therapies. DNA methylation is one					
mechanism for tumor suppre					
Because methylation is a potentially reversible mechanism for tumor suppressor gene inactivation, it is an					
intriguing target for molecular therapeutics. Drugs, such as 5-aza-deoxycytidine (DAC), are available that can					
reverse methylation changes and prevent neoplasia in vivo. Hypothesis: DNA Methylation is altered in DCIS					
1 DIDO III OII OII OII OII OII OII OII OI	with provoin moopiasia in vi	vo. rryhomesis. D	TATEMAIN	HOH IS AILEI EU III DC15	

14. SUBJECT TERMS			15. NUMBER OF PAGES
Ductal Carcinoma in si	4		
Lavage, DNA methylation			
]	,	and, doorbraine	16. PRICE CODE
17. SECURITY CLASSIFICATION	18. SECURITY CLASSIFICATION	19. SECURITY CLASSIFICATION	20. LIMITATION OF ABSTRACT
OF REPORT	OF THIS PAGE	OF ABSTRACT	
Unclassified	Unclassified	Unclassified	Imlimited

and is a therapeutic target for intraductal therapy. Specific Aim 1: Document the methylation status of tumor suppressor genes in DCIS. Specific Aim 2: Document the feasibility of an intraductal approach to DCIS. Specific Aim 3: Identify the dose(s) of DAC with biologic activity and acceptable side effects when delivered

intraductally to patients with DCIS (Phase I trial). The ultimate goal of this proposal is to evaluate DNA methylation as a target for intraductal therapy. The results of this study could revolutionize the way we treat

NSN 7540-01-280-5500

DCIS.

Standard Form 298 (Rev. 2-89) Prescribed by ANSI Std. Z39-18 298-102

Table of Contents

Cover	1
SF 298	2
Introduction	4
Body	4
Key Research Accomplishments	4
Reportable Outcomes	4
Conclusions	4
References	4
Appendices	4

Introduction: Ductal carcinoma in situ(DCIS), the preinvasive form of infiltrating ductal carcinoma of the breast, currently accounts for 20-30% of breast cancers and is treated by surgically removing the involved ducts. In DCIS, the malignant cells have not having invaded through the basement membrane and therefore have not gained access to the lymphatics or the systemic circulation. DCIS is a local disease, and so an ideal candidate for local therapies. DNA methylation is one mechanism for tumor suppressor gene inactivation. It is an early event in the course of malignant progression in several tumor systems. Because methylation is a potentially reversible mechanism for tumor suppressor gene inactivation, it is an intriguing target for molecular therapeutics. Drugs, such as 5-aza-deoxycytidine (DAC), are available that can reverse methylation changes and prevent tumor suppressor gene-related neoplasia in vivo. Hypothesis: DNA Methylation is altered in DCIS and is a therapeutic target for intraductal therapy. Specific Aim 1: To document the methylation status of a panel of tumor suppressor genes in DCIS. Specific Aim 2: Document the feasibility of an intraductal approach to DCIS. Specific Aim 3: Identify a dose or range of doses of DAC with biologic activity and acceptable side effects when delivered intraductally to patients with DCIS (Phase I trial). The ultimate goal of this proposal is to evaluate DNA methylation as a target for intraductal therapy. The results of this study could revolutionize the way we treat DCIS.

Body: Unfortunately due to significant administrative delays, no work has yet been done on this project. Despite a complete submission and completion of the responses to the Memorandum of Record from the HSRRB, no further action was taken by the original Human Subjects Protection Specialist assigned to my proposal, Margaret Abramowitz, RN. In 12/02 I was notified by Andrea Kline, the newly assigned Human Subjects Protection Specialist, that Ms. Abramowitz had nod presented my proposal and responses to the memorandum of record to the HSSRB. Ms. Kline confirmed that my file was complete and ready to go to the board. I notified Ms. Kline of my plans to change institutions and that I had initiated the process for transferring my grant to New York University. It was agreed to wait for the transfer prior to submitting my proposal to the HSRRB as the transfer would lead to a need for a new approval. The transfer process was initiated at the University of Southern California in 11/02. I left that institution on 12/31/02 and started at NYU in 01/03. To date, the transfer has not been completed and the proposal has not been given final approval by your HSRRB. Consequently, I have not been able to start the project. I am hopeful that this will be achieved in the next month or two and work can begin. Because of the delays, I am requesting an 18 month no cost extension in order to successfully complete the work.

Key Research Accomplishments:

- -Response to Memorandum of Record Complete 8/12/02.
- -No further action by Margaret Abramowitz, RN, Human Subjects Protection Specialist, AMDEX Corp.
- -12/02 Notified by Andrea Kline of Change in Human Subjects Protection Specialist from AMDEX. Told that previous specialist had never forwarded my file to the Board for review. Acknowledged that my file was complete. Ms. Kline notified of my planned move and agreed to wait until transfer granted to submit to board.
- -11/15/02 Began process of transferring grant as PI moving to NYU as of 1/1/03
- -As of 8/1/03 Grant transfer not yet accomplished

Reportable Outcomes: None

Conclusions: No work accomplished due to administrative delays. Request 18 month no-cost extension in order to complete the project.

References: N/A

14/12

Appendices: N/A